REMARKS

Claims 1-9 are pending in the instant application. Claims 1-9 have been rejected. Claim 1 and 8 have been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. §112

The rejection of claims 1-9 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention have been maintained. Claims 1-9 are drawn to a method of stably expressing a selected DNA sequence in the central nervous system of a mammal. The Examiner suggests that the specification provides no use for mere stable expression other than for gene therapy. Further, the Examiner has suggested that the specification does not disclose a use of the method of the invention in the production of an animal model.

The Applicants respectfully traverse this rejection.

Applicants believe that the specification provides sufficient guidance to one of skill in the art how to make and/or

use the invention. As set forth by MPEP 2164.01(b), the application has disclosed at least one method for making and using, *i.e.* gene therapy, the claimed invention that bears a reasonable correlation to the entire scope of the claim. While the Examiner has suggested that the Applicants have provided a post-filing use for the invention, Applicant's were making an earnest effort to demonstrate that it would have been well-known within the art at the time of filing that a method of stably expressing a selected DNA sequence in the central nervous system of a mammal would be useful in the production of an animal model as evidenced by Xing et al. ((1994) *J. Immunol.* 153:4059-4069).

MPEP 2164.01 states the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. Denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrick GMBH v. American*

Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

Further, one of skill in the art could have used the teachings of the specification coupled with information known in the art at the time of filing (for example, see Xing et al.) to also generate an animal model. As MPEP 2164.01 makes clear, any enabled use is sufficient to preclude a rejection under section 112. As in the present case, where multiple uses are supported by the specification and would have been appreciated by the skilled artisan at the time of filing, the rejection is improper.

Further, the Examiner suggests that the state of the art at the time of filing was not developed sufficiently that mere showing of delivery of a gene to a particular tissue would be viewed as enabling gene therapy. The Examiner cites the references of Verma, Marshall, Anderson and Blau, acknowledging that these references do not discuss neurotropic viruses, but do set the state of the general art of gene therapy at the time of filing.

At the onset, Applicants respectfully disagree with the Examiners view that the only use of the method of the invention is for gene therapy purposes. Without considering other uses well-known in the art at the time of filing, the Examiner

suggests that Verma, Marshall, Anderson and Blau address the general state of the art of gene therapy and that it was unpredictable with respect to neurotropic viruses. Applicants maintain that these references do not fully address the state of the art of neurotropic viruses. As Applicants have stated in arguments filed March 10, 2003 in paper no. 24, the references of Verma ((1997) *Nature* 389:239-242), Marshall ((1995) *Science* 269:1050-1055), Anderson ((September 1995) *Scientific American* 124-128), and Blau ((Nov. 2, 1995) *New Engl. J. Med.* 1204-1207) are directed to the more commonly used vector systems of the time: adenoviruses, adeno-associated viruses, retroviruses and lentiviruses, and provide a limited understanding of the art for using neurotropic viruses to deliver a transgene to the CNS.

The Examiner further cites the references of Fink et al. ((1996) *Clinical Neuroscience* 3:284-291) and Wolfe et al. ((1992) *Nature Genetics* 1:379-84) for teaching the use of HSV-1 vectors and suggests that the use of these vectors in gene therapy protocols was unpredictable. The Examiner suggests that the teachings of Fink et al. and Wolfe et al. indicate that an HSV-1-LAT vector, similar to that disclosed in the present invention, would not be useful to sufficiently express a therapeutic protein

as the expression was not long enough to correct a disease phenotype.

Applicants maintain that while Wolfe et al. indicate that too little enzyme was present for measurements of β-glucuronidase activity, they also indicate that since the intensity of staining has been shown to correlate with quantitative measurements of enzymatic activity, that the vector-corrected cells may have been expressing near normal amounts of GUSB. Furthermore, using an HSV vector of equivalent genomic structure to that taught in the instant application, the teachings of U.S. Patent No. 5,849,572 to Glorioso demonstrate that lacZ transgene expression from said vector was present even at 6 months post-inoculation and that X-gal staining increased over time (see col. 8, lines 32-35). Thus, as the present invention and prior art indicate that the length of transgene expression may exceed 6 months with demonstrable increases in expression, it would be reasonable for the skilled artisan to apply the method of the invention to gene therapy with an expectation of successfully expressing a transgene in the CNS for at least four months.

Accordingly, the Applicants believe that the application provides a sufficient description to enable one reasonably skilled in the art to make or use the invention from what is

provided in the disclosure coupled with information known in the art without undue experimentation. It is therefore respectfully requested that this rejection be withdrawn.

II. Rejection of Claims Under 35 U.S.C. §102

Claims 1, 2, 4, 5 and 6 have been rejected under 35 U.S.C. §102 (e) as being clearly anticipated by U.S. Patent No. 5,849,572 to Glorioso. The Examiner suggests that Glorioso teaches the injection of an HSV-1 vector comprising a LAT promoter operatively linked to a LacZ gene into rat hippocampus and that expression of lacZ was detected 6 months after injection into the hippocampal region of the rat brain, indicating stable expression. The Examiner further suggests that Glorioso teaches that for Parkinsonian gene therapy evaluation, an HSV-1 vector comprising the LAT promoter operatively linked to a tyrosine hydroxylase gene can be injected into rat hippocampus and thus anticipates the claimed invention. The Applicants respectfully traverse this rejection.

In an effort to further the prosecution of this application, Applicants have amended claim 1 to recite that a selected DNA sequence is stably expressed in the central nervous system of a mammal by administering to peripheral neuron cells of a mammal a

neurotropic viral vector which infects cells of the central nervous system of the mammal. Support for this amendment may be found in the paragraph bridging pages 19 and 20. While, Glorioso teaches the detection of lacZ expression from an HSV-1 vector in the hippocampal region of the rat brain, this reference does not teach administration of a neurotropic virus, which contains a selected DNA sequence operatively linked to a selected promoter, to peripheral neurons of a mammal wherein said virus infects cells of the central nervous system. Rather, this reference shows either peripheral nervous system administration via corneal scarification and subsequent transgene expression in peripheral nervous system-localized trigeminal ganglia (see col. 8, lines 27-35) or central nervous system injection into the hippocampal region and subsequent transgene expression evident in the hippocampus (see col. 7, lines 35-39 and col. 7, lines 59-62). It is therefore respectfully requested that this rejection be withdrawn.

III. Rejection of Claims Under 35 U.S.C. §103

Claims 1 and 7 have been rejected under 35 U.S.C. §103 as being unpatentable over U.S. Patent No. 5,849,572 to Glorioso in

view of Dobson et al. (1989) *J. Virol.* 63:3844-3851. The Examiner suggests it would have been obvious to the ordinary artisan to produce and stably express a transgene in the CNS using an HSV-1 vector as taught by Glorioso and substituting the HSV-1 vector of Glorioso with the HSV-1 strain 17 taught by Dobson et al. as the strains are of equivalent genomic structure.

Claims 1, 3, 8, and 9 have been rejected under 35 U.S.C. §103 as being unpatentable over U.S. Patent No. 5,849,572 to Glorioso in view of Dobson et al. (1989) *J. Virol.* 63:3844-3851 and Guise et al. (1985) *Gene* 34:105-110. The Examiner suggests it would have been obvious to the ordinary artisan to produce and stably express a β-glucuronidase, as taught by Guise et al., in the CNS using an HSV-1 vector as taught by Glorioso and substituting the HSV-1 vector of Glorioso with the HSV-1 strain 17 taught by Dobson et al. as the strains are of equivalent genomic structure.

Applicants respectfully traverse these rejections.

The primary reference of Glorioso fails to make the instant invention obvious for the same reason it does not anticipate the instant invention, it does not teach administration of a neurotropic virus to peripheral neurons with stable expression of the associated transgene in the central nervous system as recited

by amended claims 1 and 8. MPEP § 2143 states that to establish a *prima facie* case of obviousness, the prior art references when combined must teach or suggest all the claim limitations. As neither Dobson et al. nor Guise et al. show central nervous system-localized expression of a transgene delivered by a neurotropic vector via peripheral neurons, this reference fails to remedy the deficiencies of the primary reference. It is therefore respectfully requested that this rejection be withdrawn.

IV. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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